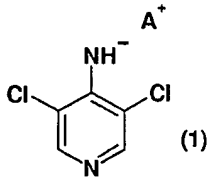
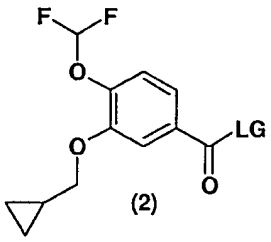
Claims

1. Process for the preparation of roflumilast by reacting the anion of 4-amino-3,5-dichloro-pyridine (1)



(1)

in which A^+ is a cation, preferably an alkali metal cation and particularly preferably a potassium cation, with an activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid (2),



(2)

in which LG is a suitable leaving group, preferably a chlorine atom, a bromine atom or a radical of the formula OC(O)-1-4C-alkyl, and particularly preferably a chlorine atom,
characterized in that the molar ratio of the employed anion of 4-amino-3,5-dichloropyridine (1) to the activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid (2) is at least 1.5 and at most 3.

2. Process according to Claim 1, characterized in that the molar ratio of the employed anion of 4-amino-3,5-dichloropyridine (1) to the activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxy-benzoic acid (2) is at least 1.8 and at most 2.7.

3. Process according to Claim 1, characterized in that the molar ratio of the employed anion of 4-amino-3,5-dichloropyridine (1) to the activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxy-benzoic acid (2) is at least 2 and at most 2.5.

4. Process according to Claim 1, characterized in that the molar ratio of the employed anion of 4-amino-3,5-dichloropyridine (1) to the activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxy-benzoic acid (2) is 2.2.

5. Process according to any of Claims 1 to 4, characterized in that the reaction of the anion of 4-amino-3,5-dichloropyridine (1) with an activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid (2) is carried out in a solvent selected from the group of dichloromethane, toluene, xylene, dimethylformamide or N-methylpyrrolidone.

6. Process according to any of Claims 1 to 4, characterized in that the reaction of the anion of 4-amino-3,5-dichloropyridine (1) with an activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid (2) is carried out in a dimethylformamide.

7. Process according to any of Claims 1 to 6, characterized in that the reaction of the anion of 4-amino-3,5-dichloropyridine (1) with an activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid (2) is carried out a temperature between 0°C and the boiling point of the inert solvent used.

8. Process according to any of Claims 1 to 6, characterized in that the reaction of the anion of 4-amino-3,5-dichloropyridine (1) with an activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid (2) is carried out a temperature between 20°C and 30°C

9. Process according to any of Claims 1 to 8, characterized in that the activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid (2) is 3-cyclopropylmethoxy-4-difluoromethoxy-benzoyl chloride.

10. Process according to any of Claims 1 to 8, characterized in that the activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid (2) is 3-cyclopropylmethoxy-4-difluoromethoxy-benzoyl bromide.

11. Process according to any of Claims 1 to 8, characterized in that the activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid (2) is a 3-cyclopropylmethoxy-4-difluoromethoxy-benzoic acid 1-4C-alkyl-ester.

12. Process according to any of Claims 1 to 11, characterized in that a strong base selected from the group of KOtBu, NaOtBu and LiOtBu is used to prepare the anion of 4-amino-3,5-dichloropyridine.

13. Process according to Claim 12, characterized in that KOtBu is used to prepare the anion of 4-amino-3,5-dichloropyridine (1).

14. Process according to any of Claims 1 to 13, characterized in that the product resulting from the process is recrystallized in a mixture of isopropanol and water (ratio isopropanol/water: between 85:15 and 100:0% by volume, preferably between 90:10 and 95:5% by volume).

15. Roflumilast prepared by a process according to any of Claims 1 to 14.

16. Roflumilast prepared by a process according to any of Claims 1 to 14, characterized in that the purity is ≥ 99% by weight, preferably ≥ 99.8% by weight.

17. Roflumilast prepared by a process according to any of Claims 1 to 14, characterized in that it contains less than 0.1% by weight, preferably less than 0.05% by weight, of the by-product N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-hydroxybenzamide.

18. Roflumilast prepared according to Claim 15, 16 or 17 for use in the treatment of diseases.

19. Pharmaceutical compositions containing roflumilast prepared according to Claim 15, 16 or 17 together with conventional pharmaceutical auxiliaries and/or excipients.

20. Use of the roflumilast prepared according to Claim 15, 16 or 17 for the production of pharmaceutical compositions for the treatment of an acute or chronic airway disorder, a dermatosis or an arthritic disorder.

21. Method for the treatment of mammals, including humans, suffering from an acute or chronic airway disorder, a dermatosis or an arthritic disorder, characterized in that a therapeutically effective amount of the roflumilast prepared according to Claim 15, 16 or 17 is administered together with conventional auxiliaries and/or excipients to the mammal with the disorder.